

5 more activity than the cognate, wild-type protein; and (d) expressing the selected variant regulator protein in a cell, thereby increasing production of the secondary metabolite in the cell.

10 In certain embodiments of the fourth aspect, the cell is a fungal cell. In certain embodiments of the fourth aspect, the protein regulator of secondary metabolite production is a transcription factor. In certain embodiments of the fourth aspect, the protein regulator of secondary metabolite production is a transmembrane

15 transporter, a protein that mediates secretion, a kinase, a G-protein, a cell surface receptor, a GTPase activating protein, a guanine nucleotide exchange factor, a phosphatase, a protease, a phosphodiesterase, a bacterial protein toxin, an importin, an RNA-binding protein, an SCF

20 complex component, an adherin, or a protein encoded within a biosynthetic cluster. In certain embodiments of the fourth aspect, the cell is a heterologous cell, preferably selected from the group consisting of *S. cerevisiae*, *E. coli*, *A. nidulans*, *Candida sp.*, and *N. crassa*. In certain

25 other embodiments of the fourth aspect, the cell is a homologous cell, preferably selected from the group consisting of *Aspergillus sp.*, *Penicillium sp.*, *Acremonium chrysogenum*, *Yarrowia lipolytica*, *Nodulisporium sp.*, *Fusarium sp.*, *Monascus sp.*, *Claviceps sp.*, *Trichoderma*

30 *sp.*, *Tolypocladium sp.*, *Tricotheicium sp.*, *Fusidium sp.*, *Emericellopsis sp.*, *Cephalosporium sp.*, *Cochliobolus sp.*, *Helminthosporium sp.*, *Agaricus brunescens*, *Ustilago maydis*, *Neurospora sp.*, *Pestalotiopsis sp.*, and *Phaffia rhodozyma*.

35 In certain other embodiments of the fourth aspect, the cell is a heterologous cell and the method further comprises expressing the variant regulator protein in a homologous cell, thereby increasing secondary metabolite production in the homologous cell. In certain embodiments

40 thereof, the heterologous cell is an organism selected from the group consisting of *S. cerevisiae*, *E. coli*, *A.*

5 *nidulans*, *Candida sp.*, , and *N. crassa* and the homologous cell is an organism selected from the group consisting of *Aspergillus sp.*, *Penicillium sp.*, *Acremonium chrysogenum*, *Yarrowia lipolytica*, *Nodulisporium sp.*, *Fusarium sp.*, *Monascus sp.*, *Claviceps sp.*, *Trichoderma sp.*,
 10 *Tolytocladium sp.*, *Tricotheicium sp.*, *Fusidium sp.*, *Emericellopsis sp.*, *Cephalosporium sp.*, *Cochliobolus sp.*, *Helminthosporium sp.*, *Agaricus brunescens*, *Ustilago maydis*, *Neurospora sp.*, *Pestalotiopsis sp.* and *Phaffia rhodozyma*.

15 In a fifth aspect, the invention provides an isolated variant regulator protein of secondary metabolite production having increased activity compared to a cognate, wild-type protein, made by the process comprising: (a) selecting a nucleic acid comprising a
 20 polynucleotide encoding a protein regulator of secondary metabolite production; (b) mutating the nucleic acid to create a plurality of nucleic acid molecules encoding variant regulator proteins of secondary metabolite production; (c) selecting a variant regulator protein with
 25 more activity than the cognate, wild-type protein; and (d) recovering the selected variant regulator protein.

In certain embodiments of the fifth aspect, the variant regulator protein selected has more activity in a fungal cell. In certain embodiments of the fifth aspect,
 30 the protein regulator of secondary metabolite production is a transcription factor. In certain embodiments of the fifth aspect, the protein regulator of secondary metabolite production is a transmembrane transporter, a protein that mediates secretion, a kinase, a G-protein, a
 35 cell surface receptor, a GTPase activating protein, a guanine nucleotide exchange factor, a phosphatase, a protease, a phosphodiesterase, a bacterial protein toxin, an importin, an RNA-binding protein, an SCF complex component, an adherin, or a protein encoded within a
 40 biosynthetic cluster. In certain embodiments of the fifth aspect, the variant regulator protein selected has

5 more activity in a heterologous cell, preferably selected from the group consisting of *S. cerevisiae*, *E. coli*, *A. nidulans*, *Candida sp.*, *Neurospora sp.*, *Pestalotiopsis sp.*, and *N. crassa*. In certain embodiments of the fifth aspect, the variant regulator protein selected has more
 10 activity in a homologous cell, preferably selected from the group consisting of *Aspergillus sp.*, *Penicillium sp.*, *Acremonium chrysogenum*, *Yarrowia lipolytica*, *Nodulisporium sp.*, *Fusarium sp.*, *Monascus sp.*, *Claviceps sp.*, *Trichoderma sp.*, *Tolypocladium sp.*, *Tricotheicium sp.*,
 15 *Fusidium sp.*, *Emericellopsis sp.*, *Cephalosporium sp.*, *Cochliobolus sp.*, *Helminthosporium sp.*, *Agaricus brunescens*, *Ustilago maydis*, *Neurospora sp.*, *Pestalotiopsis sp.*, and *Phaffia rhodozyma*.

In certain embodiments of the fifth aspect, the
 20 variant regulator protein selected has more activity in a homologous cell and a heterologous cell. In embodiments thereof, the heterologous cell is an organism selected from the group consisting of *S. cerevisiae*, *E. coli*, *A. nidulans*, *Candida sp.*, *Neurospora sp.*, *Pestalotiopsis sp.*,
 25 and *N. crassa* and the homologous cell is an organism selected from the group consisting of *Aspergillus sp.*, *Penicillium sp.*, *Acremonium chrysogenum*, *Yarrowia lipolytica*, *Nodulisporium sp.*, *Fusarium sp.*, *Monascus sp.*, *Claviceps sp.*, *Trichoderma sp.*, *Tolypocladium sp.*,
 30 *Tricotheicium sp.*, *Fusidium sp.*, *Emericellopsis sp.*, *Cephalosporium sp.*, *Cochliobolus sp.*, *Helminthosporium sp.*, *Agaricus brunescens*, *Ustilago maydis*, *Neurospora sp.*, *Pestalotiopsis sp.*, and *Phaffia rhodozyma*.

In yet another embodiment of the fifth aspect, the
 35 variant regulator protein is a variant protein of the lovE protein having at least one of the following mutations:
 (1) a Group 6 amino acid residue mutated to a Group 2 amino acid residue at position 31, for example, the mutation represented by F31L; (2) a Group 3 amino acid
 40 residue mutated to a Group 5 amino acid residue at position 41, for example, the mutation represented by Q41K